OPINION

Rethinking clinical trials for cytostatic drugs

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The failure of many cytostatic agents in Phase III clinical trials for treatment of common cancers has led researchers to question current approaches to trial development. Recent studies offer some clues as to what is wrong with two particular aspects of clinical trial design — survival as an end point and simultaneous combination with cytotoxic chemotherapy — and indicate possible alternatives.

Cytotoxic chemotherapy has been the mainstay of medical approaches to the treatment of solid cancers. More recently, novel non-cytotoxic agents that have many different mechanisms of action have been investigated. These are commonly referred to as 'cytostatic' agents — drugs that are characterized by their ability to inhibit tumour growth without direct cytotoxic activity towards cancer cells. These types of drugs require different development strategies than cytotoxic chemotherapeutics. For example, they are not necessarily most effective at the maximum tolerated dose.

Over the past decade, research and development of cytostatics has been the subject of considerable debate. Despite the search for novel valid surrogate markers of biological and antitumour activity, tumour response and PROGRESSION-FREE SURVIVAL are still the only widely accepted means of measuring drug efficacy. These drugs are also commonly tested in patients with late-stage disease — often with considerable uncertainty regarding optimal dose selection. Furthermore, the investigational drugs are frequently administered simultaneously with cytotoxic chemotherapy. These approaches, however, have continued to produce negative results. As trials cover long time periods and development costs are high, urgent reconsideration is necessary to avoid impeding further progress. So, what are the specific problems with trial design for cytostatic agents, regardless of drug mechanism, and what are some possible solutions?

History

With the exception of hormonal therapies, the vast majority of established anticancer drugs are cytotoxic agents that are designed to kill cancer cells, thereby eradicating or shrinking tumours — this effect is known as 'tumour response'. Tumour shrinkage, which is relatively simple to document, has been the common end point in clinical trials with these agents. Unfortunately, in patients with advanced forms of many common solid tumours, even though cytotoxic drugs can shrink the tumour completely, it usually recurs. Frequently, no survival benefit is observed and these therapies are often associated with substantial toxicity.

Over the past decade, a range of cytostatic drugs have been developed that are designed to interfere with one or more of the many molecular mechanisms that drive tumour growth. It has been hoped that such agents would have low toxicity and prolong survival, allowing patients to 'live with their cancer'. In practice, however, it has proven to be much more difficult to demonstrate this inhibition of growth by cytostatic drugs than to demonstrate shrinkage of tumours with cytotoxic chemotherapeutics. It is unclear whether this is due to a lack of drug efficacy or inappropriate clinical trial methodologies.

Researchers performed some of the first clinical trials with cytostatics in the mid-1990s. For example, the matrix metalloproteinase inhibitor BB2516 (marimastat) was tested in patients with cancers of the pancreas, ovary, colorectum, stomach and prostate. Whereas Phase II data, based on changes in the level of tumour-associated proteins, were encouraging[1], ultimately these results were misleading and the development of marimastat was subsequently ceased. These efforts coincided with the development of the newer cytotoxic agents, such as docetaxel (for breast cancer), topotecan (for ovarian cancer) and gemcitabine (for pancreatic cancer). Trials with docetaxel and topotecan only reported tumour response rates when they were administered as second-line therapies; these outcomes served as the basis for marketing approval[2,3] — survival data followed this approval. The clinical research programmes for cytotoxic agents such as these, which were typical at the time, are summarized in TABLE 1.

Gemcitabine, when approved in 1997, was the exception to this approach. The drug was compared to the chemotherapeutic agent 5-fluorouracil (5-FU) (REF. 4) in a trial of 126 patients with pancreatic cancer. The primary end point was 'clinical benefit response' (CBR) — an algorithmic composite of symptoms and performance — with a secondary end point of OVERALL SURVIVAL. A total of 14 of 63 patients on gemcitabine showed CBR, compared to 3 of 63 patients who were treated with 5-FU. Although this result was statistically significant, it was also controversial. It was widely considered that the more convincing evidence of this drug's effect (and the basis for its approval) was the statistically significant increase in median survival time to 5.7 months in patients who received the drug, versus 4.2 months in patients in the control group.

Following the development of gemcitabine, survival studies became the accepted standard, if not essential, method of confirming cancer drug efficacy. A summary of recent clinical trial data for several cytotoxic agents is shown in TABLE 2. Although it is good to have new agents with well-defined efficacy, their adoption into standard clinical practice causes problems for cytostatics, in that only patients with advanced disease who have already been treated with other drugs become eligible for trials. This occurs despite warnings that tumours weighing several hundred grams with well-developed blood supplies are unlikely to respond to any type of drug. Investigators who design clinical trials have dealt with this by combining the test reagent with first-line chemotherapy, and comparing the response of the combination to patients who received chemotherapy plus placebo. Advantages to this approach include earlier intervention with the investigational drug, the ability to test the drug in patients who have lower tumour burdens and are less likely to have drug-resistant tumours, and extension of the maximum duration of treatment.

There were other factors in trial design that made it difficult to detect the efficacy of cytostatics. For example, cytotoxics are typically administered in short courses of maximal doses, with expected immediate effects. This is not necessarily appropriate for cytostatics, which can require long-term therapy and for which it is often difficult to determine the most effective dosage. Whereas tumour shrinkage has been clearly documented in patients who were treated with cytostatic agents such as the epidermal growth factor (EGF) receptor inhibitors trastuzumab

Table 1 | Clinical trial programme for cytotoxic drugs before the mid-1990s

Phase	Patient number and type	Result
I	15–30 patients with late-stage cancers of all types	Determining optimal dose (maximum tolerated dose of bolus or short treatment course)
II*	30–100+ patients undergoing second-line therapy for a single tumour type; some comparative studies	Confirming antitumour activity by determining response rate and duration
III (or IV, post-marketing)	~100–300 patients undergoing first-line, combination therapy	Determining response rates, time of progression-free survival and overall survival

*Consider submission for marketing approval based on response data.

(Herceptin) and gefitinib (Iressa), the tumour response to these drugs is less than for cytotoxic drugs. In fact, the only cytostatic agent found to produce an immediate effect on a solid tumour in a manner similar to that of cytotoxic agents was imatinib (Glivec), for the treatment of gastrointestinal stromal tumours (GISTs) (see below). On the other hand, patients treated with cytostatic drugs might achieve states of 'stable disease', which is an acceptable, though difficult to characterize, outcome.

To counter these difficulties in measuring efficacy, alternate 'surrogate markers' of clinical benefit were investigated (TABLE 3). However, no markers other than response and progression-free survival have been successfully used to secure drug registration. This could be due to variations in the levels and characteristics of known surrogate markers throughout tumour progression. However, the use of some SURROGATE END POINTS in cancer clinical trials is gaining support. For example, positron emission tomography (PET) has been used to track therapeutic efficacy in patients with lung, head and neck cancer, and, most recently, in patients with GISTs. These results have been striking, as changes in the uptake of ^{18}F-fluoro-2-deoxy-D-glucose (18FDG), a common radiotracer, are closely correlated with changes in tumour behaviour and clinical outcome[5]. Measurements of tumour blood flow, via dynamic magnetic resonance imaging (MRI) and colour Doppler imaging (CDI), in dose-ranging studies have also shown promise in determining the efficacy of anti-angiogenic agents such as vascular endothelial growth factor (VEGF) receptor inhibitors[6].

So, in most trials that are designed to test cytostatics, if the tumour response rate is the only factor used to measure the efficacy of a drug, the drug's true benefit can be underestimated. Determination of progression-free survival could therefore be the only clinical trial end point that truly reveals the efficacy of a cytostatic agent. In this case, documentation of stable disease becomes crucial, but is difficult, time consuming and expensive, and is usually declined in favour of the much simpler assessment of overall survival. Clinical investigators have been led into trial designs that involve the co-administration of cytostatics with cytotoxics, with overall survival as the primary determinant of outcome.

Overall survival

Duration of patient survival is considered the most reliable and clinically relevant outcome in trials of patients with life-threatening diseases. This end point is almost entirely free of bias, with appropriate randomization, and is generally easy to record. The phrase 'if a cancer drug doesn't make you live longer, it can't be much use' is commonly heard and is very hard to argue against, even though survival depends on factors other than the trial drug.

Survival trials are typically very large and cover long time periods. Long-term studies were almost inconceivable in the early 1990s, when trials typically only involved a few hundred patients or less. Measuring survival responses of patients with early-stage cancers can require 10 years and thousands of patients — well outside feasible limits for an unregistered drug. In trials such as these, patients must also be free to seek other treatments when their cancers progress. The impact of patient cross-over — to the control arm or to other therapies — inevitably dilutes any detectable difference in overall survival. So these trials become, in reality, a comparison of immediate versus delayed use of the test reagent.

For example, in patients with advanced breast cancer, trials with the anti-ERBB2 (also known as anti-HER2/neu) antibody trastuzumab (compared with placebo)[7], and trials with the aromatase inhibitor letrozole[8] (compared with the oestrogen antagonist tamoxifen) have shown pronounced differences in progression-free survival. They have not, however, shown such large differences in overall survival — probably because patients crossed from one arm of the study to another following disease progression. So, despite the difficulties in documentation, progression-free survival is a more robust assessment of drug efficacy than overall survival, and is particularly well suited for measuring efficacy of cytostatic agents.

Despite these important issues, increased overall survival has become the 'gold standard' of trial success. However, until the recent results with bevacizumab (Avastin)[30], the monoclonal antibody against VEGF, all of the large trials of cytostatics reported over the last 12 months have failed to show an increase in overall survival (TABLE 4). It could be that these studies have correctly identified ineffective drugs, but the possibility of 'false negatives' must be considered, as all the drug candidates were developed with good rationale and strong animal data, and all produced tumour shrinkage or stabilization in Phase II studies.

Recent survival studies of drugs with previous proven efficacy have produced apparently negative results and demonstrate that false-negatives can easily occur (TABLE 4). One of these is the recent International Collaborative Ovarian Neoplasm Group (ICON-3) study of ovarian cancer patients[9]. This study showed that adding paclitaxel to

Table 2 | Clinical trial data for cytotoxic agents

Agent	Cancer type	Result	References
Docetaxel	Breast	Complete and partial responses; no survival data	2
Topotecan	Ovarian	Complete and partial responses; increased overall survival	3
Gemcitabine	Pancreatic	Increased clinical benefit response; increased overall survival	4
Irinotecan	Colorectal	Complete and partial responses; increased overall survival	23
Capecitabine	Colon	Complete and partial responses; increased overall survival; progression-free survival	24
	Breast	Complete and partial responses; increased overall survival; progression-free survival	

Table 3 | Surrogate markers

Marker	Comments	References
Clinical symptoms of biological activity (limb-girdle musculoskeletal symptoms with matrix metalloproteinase inhibitors, dermatitis and diarrhoea with EGFR inhibitors)	Poorly quantified and unpredictable variations in effects; could have little relevance to the actual biological target	
Levels of 'cancer antigens' (CEA, CA-125, CA-19-9 and PSA)	Variability confounds interpretation; PSA and CA-125, although approved for clinical monitoring of patients, are not valid surrogates for clinical trials	
Molecular products of tumour progression (pyridinoline cross-links, carboxy-terminal peptides) and enzymtic markers of cancer progression (alkaline phosphatase, lactate dehyrogenase)	Of prognostic value, although not useful for determining drug activity; bisphosphonate levels are useful markers of bone breakdown, although no clear link is established with clinical outcome	25,26
Tumour shrinkage	Widely accepted, although relationship to clinical outcome still debated; FDA reports that 73% of cancer drug approvals in the past 10 years were based on radiological response; clear improvements observed after treatment with cytostatics and identified through PET analysis, but without any radiological documentation of tumour shrinkage	5
Tumour stabilization, disease-free or progression-free interval	Difficulties in documentation and variations in definitions, but can be powerful, as for trastuzumab	7
Measurements of tumour metabolism and blood flow (PET, colour Doppler, dynamic MRI analysis)	Becoming increasingly useful, although predictive value remains unclear; practicality challenges in clinical setting	
Tumour histology	Although effective drugs must affect histology, standardizing biopsy data is challenging; biopsy established as a critical component of early trials	
Non-tumour histology (skin biopsy after treatment with angiogenesis inhibitors)	Useful in determining biological activity of drug (gefitinib); not useful in predicting patient response	27,28
Number of cancer cells in the blood	Required in assessing haematological malignancy; has helped greatly in development of imatinib for the treatment of chronic myeloid leukaemia; use in monitoring of solid cancers not clear	

CA, Cancer antigen; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; FDA, Food and Drugs Administration; MRI, magnetic resonance imaging; PET, positron-emission tomography; PSA, prostate-specific antigen.

carboplatin produced no benefit in overall survival or progression-free survival over carboplatin alone, which could be taken as an indication that paclitaxel is ineffective. Paclitaxel, however, is widely acknowledged to be an effective treatment for ovarian cancer. This result demands consideration of the possibility that survival as a measure of outcome, when one treatment is administered simultaneously with another to 'optimize' chemotherapy, can make an active drug look ineffective. In the case of paclitaxel, this is a point of debate for academics and a source of considerable frustration for the manufacturers. However, for a novel drug in Phase III development, this outcome would be a disaster. So, why don't these trial designs always work as predicted?

Cytostatic–cytotoxic synergy

Potential synergistic activity between cytostatic and cytotoxic agents is usually first examined in animal models. After preclinical studies of gefitinib, headlines reported that animal studies[10] showed that the drug had synergistic effects with cytotoxic agents. Similar announcements accompanied the reports of animal studies involving another EGF receptor inhibitor, erlotinib (Tarceva)[11]. It is dangerous, however, to assume that drugs that act in synergy in animal studies will also do so in humans.

Cytotoxic agents are not generally tolerated by animals at doses high enough to shrink tumours, whereas in patients, very high doses can be administered with the help of intensive supportive measures. Moreover, some cytostatic agents function by decreasing the rate of cancer-cell proliferation, whereas many cytotoxic drugs depend on cell proliferation for their antitumour effects. So, although an 'additive' effect is observed when cytotoxics are given at low doses (that is, in animal studies), this synergy is lost when drugs are administered at high doses. Furthermore, although toxic interactions might not be detected when agents are administered at low doses in animals, they might become evident when administered to humans at higher doses. Finally, the pharmacodynamic potential of one drug to cancel the effect of the other, such as the ability of angiogenesis inhibitors to reduce cytotoxic drug delivery to the tumour, can be overlooked in short-term animal studies.

Further evidence that combination studies do not always reveal the efficacy of their single agents comes from trials with tamoxifen. Although tamoxifen is not usually considered to be a cytostatic agent, it functions by blocking signalling pathways that promote cellular proliferation. A decade-long study on the effects of treating breast cancer patients with a combination of tamoxifen and chemotherapy was reported at the American Society of Clinical Oncology (ASCO) last year[12]. In this study, patients with breast cancer were randomized and received either tamoxifen alone, tamoxifen during and after treatment with chemotherapy, or tamoxifen after chemotherapy was finished. The authors reported that the group that received tamoxifen after chemotherapy had the greatest 8-year progression-free survival, compared with patients that received tamoxifen alone or with concurrent chemotherapy. Furthermore, administration of tamoxifen concurrently with cytotoxic chemotherapy seemed to have deleterious effects, compared with tamoxifen treatment alone. This loss of efficacy could be a specific feature of tamoxifen, or reflect a broader concern that applies to other cytotoxic–cytostatic combinations.

On the other hand, a study of the combined effects of treatment with trastuzumab and cytotoxic drugs showed clear beneficial effects on tumour response, progression-free survival and overall survival[7], as is apparently the case with recent results on bevacizumab

(see Trial Watch on page 471 of this issue). So, concerns about drug combination trials might only be applicable to certain cytostatics, or cytostatics with certain mechanisms.

Toxicity of combined therapy

Although trastuzumab was shown to have remarkable synergy with chemotherapeutics such as anthracyclines, patients treated with both drugs also had a high incidence of cardiac toxicity. The cardiotoxic effects of anthracyclines are well known, and can be controlled by careful dose monitoring. The addition of traztuzumab to anthracycline therapy, however, increased the percentage of patients that experienced cardiotoxicity from 3% to 16%. Subsequent studies showed that ERBB2 is required for normal cardiac development and function, so its inhibition can facilitate anthracycline-induced cardiotoxicity[13].

Simultaneous administration of gefitinib with cytotoxic drugs has also been shown to cause fatal multifocal ulcerative enteritis[10], necessitating dose reduction of gefitinib. In a Phase III study comparing the effect on survival of gefitinib to placebo as add-on therapy to gemcitabine and cisplatin[14], up to 60% of patients that received both drugs developed diarrhoea. Side effects such as this could have adverse effects on patient compliance, drug dosage, drug absorption and overall health. Furthermore, a Phase I dose-finding study[15] of the anti-VEGF receptor small molecule SU-5416, when given in combination with cisplatin and gemcitabine, caused dose-related thromboembolism in 8 of 19 patients. These effects were not seen in patients who received monotherapy with SU-5416 — even at much higher doses.

It seems reasonable to consider that cytostatic agents that target factors such as EGF and VEGF, which are involved in the recovery of gut and vascular endothelium, respectively, are required for these normal tissues to recover from chemotherapy-induced damage, and therefore suitable care should be taken if these drugs are to be taken simultaneously. So, synergistic toxicity could depend on cytostatic drug mechanisms. Contrary to the apparently prevailing view, it cannot be assumed that cytostatics will invariably act in synergy with cytotoxic agents — concurrent delivery of both types of drugs can have detrimental outcomes.

Predicting drug response

Advances in genomics and molecular analysis of tumours have improved our ability to select patients that are likely to respond to a particular therapeutic agent. For example, it is possible to select patients that are most likely to respond to trastuzumab based on *ERBB2* expression levels. However, it has been a challenge to identify patients that are most likely to respond to other cytostatics, as most tumours are very heterogeneous. What has also become apparent is that expression of a particular drug target does not necessarily mean that it is functionally important. For example, the EGF receptor tyrosine kinases have been widely implicated in various malignancies, and as such have represented attractive targets for novel anticancer therapies. However, although dysregulation of EGF receptor signalling is likely to contribute to tumour pathogenesis, confirmation of the expression of this receptor does not necessarily reflect the activity of this signal-transduction pathway. The recent failure of the EGF receptor inhibitor gefitinib in clinical trials of patients with non-small-cell lung cancer[14] could be due to the fact that this agent is only likely to have benefit in a minority of patients — those whose tumours require activation of the EGF pathways for growth.

Conversely, the remarkable success of the tyrosine kinase inhibitor imatinib in the treatment of patients with GISTs[16] has shown that targeted therapies can be effective. GISTs are relatively homogeneous tumours, in terms of molecular pathology, in that they almost all overexpress a constitutively active mutated form of the kinase c-KIT. This would explain the high response rates of most patients to this drug. Some GISTs, however, only express wild-type KIT, but still respond to imatinib therapy[17]. This phenomenon was explained by the fact that these tumours also express a mutant form of the related receptor tyrosine kinase, platelet-derived growth factor (PDGF) receptor-α, also targeted by imatinib. Furthermore, imatinib has been shown to be effective in treating the rare tumour dermatofibrosarcoma protuberans[18], which expresses a *Col1–PDGF* fusion gene that causes constitutive PDGF receptor activation. So, drug response depends not only on the expression, but also on the activity of the drug target. This presents a significant problem for clinical trial design of protein kinase inhibitors, as it is difficult to measure the levels of signal activation in many tumour types, as well as the effects of therapeutic intervention.

The importance of selecting patients that are most likely to respond to a molecularly targeted therapy has been graphically illustrated in a recent statistical study[19]. The efficacy of a drug can be almost completely occluded by including patients in the trial who were never likely to respond to the therapy. So it is imperative to identify suitable patients at the earliest stages of clinical development. Microarray selection methods, such as those recently reported by Van de Vijver *et al.*[20], are an attractive starting point for selecting patients with tumours that are most likely to respond to a targeted therapy.

Table 4 | Results of clinical trials with cytostatic and cytotoxic agents

	Cancer type	Number of patients	Chemotherapy control	Result	References
Cytostatic agents					
SU-5416	Colorectal	1,300	Irinotecan, 5-FU and LV	No survival advantage	
Gefitinib	NSCLC	1,093	Cisplatin and gemcitabine	No survival advantage	14
Gefitinib	NSCLC	1,037	Carboplatin and paclitaxel	No survival advantage	
R115777	Pancreatic	688	Gemcitabine	No survival advantage	
R115777	Colorectal	368	Irinotecan, 5-FU and LV	No survival advantage	
Bevacizumab (Avastin)	Breast	462	Capecitabine	No survival advantage	
Cytotoxic agents					
Paclitaxel	Ovarian	2,074	Cisplatin	No survival advantage	9
Paclitaxel; docetaxel; gemcitabine	NSCLC	1,207	Cisplatin or carboplatin	No survival advantage	29

NSCLC, non-small-cell lung carcinoma; 5-FU, 5-fluorouracil; LV, leucovorin.

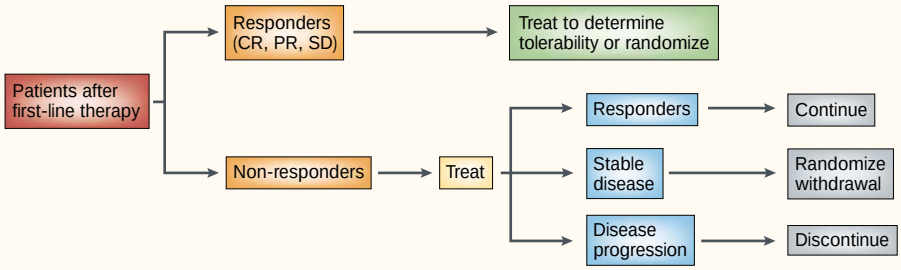

Figure 1 | **Scheme for clinical trials of cytostatic agents as monotherapy.** Patients are recruited to the trial after completing first-line chemotherapy, regardless of response. Patients who have undergone either complete response (CR), partial response (PR) or stable disease (SD) can next receive either placebo or the test drug, comparing the effect on disease progression. Patients with disease progression during first-line therapy (non-responders) would also be treated with the test agent. If a greater than 15% response rate is determined, this might be sufficient for drug registration, if no other effective therapy exists. It would also be encouraging if a large number of patients experienced stable disease (after undergoing disease progression on chemotherapy). This could, however, be due to late effects of chemotherapy — this could be tested by randomizing some patients from the test drug to placebo, then comparing rates of maintenance of disease stability. Patients who undergo disease progression after switching to placebo can go back onto therapy. Patients who undergo disease progression on the test agent would leave the study and be free to seek other therapy. This clinical trial scheme is adaptable for early- or late-stage designs, including patients with minimal disease, and avoids combination with cytotoxic chemotherapy.

Future directions

Analysis of cancer clinical trial recent successes and failures has revealed important factors to consider in designing future studies. Animal models of cancer must be relevant to the human situation and, in studies of synergistic efficacy, cytotoxic agents should be tested at clinically relevant doses. Combinations that are found to be effective should be compared with the maximally effective dose of monotherapy of each agent. Furthermore, synergistic toxicity of the combination should be carefully considered and investigated.

Early trials of a cytostatic must determine the most effective dose of monotherapy and the rate, if any, of tumour responses and disease stabilization. Dose selection decisions should be based on effect, rather than the maximally tolerated dose. Patient and tumour characteristics that can predict response to treatment must also be investigated with pre- and post-treatment biopsies if possible. If responders can be characterized, it is clear that these must be preferentially selected, and the use of BAYESIAN STATISTICAL METHODS should be considered to allow smaller patient numbers for investigation of both dose and prediction of responders.

The documentation of stable disease is not straightforward and interpretation is controversial for many reasons, including the highly stochastic nature of normal tumour progression, variability in radiographic techniques and specific clinical trial issues related to timing of investigations. Lead-time bias, in which the time from diagnosis before intervention can confound analysis, can be addressed by adequate trial size and the use of randomization techniques such as minimization. The selection of tumours documented to progress during first-line therapy ought to increase confidence that stabilization during subsequent treatment with a trial agent is a genuine effect. This could be confirmed by randomizing patients with apparently stabilized disease to withdraw or continue treatment, a concept that has been reviewed elsewhere[21]; maintenance of stabilization associated with therapy would prove a genuine treatment effect. A suitable schematic basis for clinical trials is shown in FIG 1.

Regulatory considerations. Federal regulators have shown increasing willingness to engage in debate over clinical trial design and outcome measurements. A recent publication[22] by the US Food and Drug Administration (FDA) was quoted at the recent Oncologic Drugs Advisory Committee meeting on gefitinib: "It is often misstated in media or literature that FDA only approves cancer drugs based on survival … this is clearly not the case … since 1990 … 73 percent of all approvals were not based on survival". The onus is on those involved in the development of cytostatic agents to take advantage of this attitude, accept that studies of combination agents can be unsuccessful when overall survival is used as an end point, and design trials that utilize progression-free survival as a surrogate end point. If physicians, industry and regulators cannot improve the anticancer drug trial design, as well as data review methods, then successful development and, ultimately, access to these agents will continue to be hampered.

Glossary

BAYESIAN STATISTICAL METHODS
Statistical methods in which expectation and ongoing observation are used to increase efficiency and reduce the number of observations (patient numbers) that are necessary to reach reliable conclusions. These are particularly efficient compared with 'frequentist' statistical approaches when multiple decisions are necessary — for example, in dose comparisons.

OVERALL SURVIVAL
The duration for which a patient with cancer survives after the start of treatment.

PROGRESSION-FREE SURVIVAL
The duration for which a patient with cancer survives after the start of treatment without evidence of disease progression.

SURROGATE END-POINT
A biomarker that is used to monitor disease progression and expected to predict clinical benefit based on epidemiological, therapeutic, pathophysiological or other scientific evidence.

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DATABASES

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